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Lighting up the clock

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Chapter 4

Time-of-day-dependent effects of bright light exposure on human psycho-physiology: comparison of daytime and nighttime exposure

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Abstract

Bright light can influence human psychophysiology instantaneously by inducing endocrine (suppression of melatonin, increasing cortisol levels), other physiological changes (enhancement of core body temperature), and psychological changes (reduction of sleepiness, increase of alertness). Its broad range of action is reflected in the wide field of applications, ranging from optimizing work environment to treating depressed patients. For optimal bright light application and understanding its mechanism, it is crucial to know whether its effects depend on the time of day. In this paper we report the effects of bright light given at two different times of day on psychological and physiological parameters. 24 subjects participated in two experiments (N=12 each). All subjects were non-smoking, healthy young males (18-30 years). In both experiments subjects were exposed to either bright light (5000 lux) or dim light < 10 lux (control condition) either between 12 p.m. and 4 p.m. (experiment A) or between midnight and 4 a.m. (experiment B). Hourly measurements included salivary cortisol concentrations, ECG, sleepiness (Karolinska Sleepiness Scale), fatigue and energy ratings (Visual Analogue Scale). Core body temperature was measured continuously throughout the experiments. Bright light had a time dependent effect on heart rate and core body temperature, *i.e.*, bright light exposure at night, but not in daytime increased heart rate and enhanced core body temperature. It had no significant effect at all on cortisol. The effect of bright light on the psychological variables was time independent, as nighttime as well as daytime bright light reduced sleepiness and fatigue significantly and similarly.

Introduction

Bright light is a prominent agent to influence human psychophysiology. Besides the ability to reset or shift the biological clock (Honma and Honma, 1988; Minors et al., 1991; Beersma and Daan, 1993; 2001; Rüger et al., 2003; Khalsa et al., 2003), bright light is thought to have an immediate activating effect on the central nervous system. This immediate effect has been studied mostly in the context of prolonged wakefulness to explore beneficial effects of bright light on alertness and performance, for instance in shift workers. Nighttime bright light exposure is known to reduce sleepiness (Campbell et al., 1995; Cajochen et al., 2000; Rüger et al., 2003), enhance alertness (Badia et al., 1990; Campbell and Dawson, 1990; Badia et al., 1991; Dawson and Campbell, 1991; Myers and Badia, 1993), and to improve mood and performance in healthy subjects (Daurat et al., 1993; Foret et al., 1998; Partonen and Lonnqvist, 2000). At the same time it suppresses melatonin, enhances core body temperature, and increases heart rate (Lewy et al., 1980; Saito et al., 1996; Scheer et al., 1999; Rüger et al., 2003). As the reduction of sleepiness is often accompanied by the suppression of nocturnal melatonin and/or the increase in core body temperature, it is sometimes assumed that melatonin is the causal factor in this process (Badia et al., 1993; Gilbert et al., 1999). However, data from daytime bright light exposure studies show that bright light can reduce sleepiness even though melatonin is virtually absent and core body temperature is nearly constant (Rüger et al., 2002; Phipps-Nelson et al., 2003). We have shown that the relation between melatonin suppression and reduction of sleepiness/fatigue is weak and therefore melatonin suppression cannot be the sole explanation for the activating properties of bright light (Rüger et al., 2005, in press).

Few studies have focused on the effects of light on the autonomic nervous system. The results of these studies are moreover difficult to compare as they vary greatly in the amount of light used and in output variables measured. Saito et al. (1996) and Scheer et al. (1999) showed an increase in muscle sympathetic nerve activity and heart rate in response to bright light and Gilbert and co-workers (1999) found a reduction of the heart rate of healthy young males after the administration of exogenous melatonin (5 mg) during the afternoon. Burgess et al. (2001) failed to find a clear effect of bright light on cardiac output measures such as Respiratory Sine Arhythmia, Pre-ejection period, and Diastolic Blood Pressure. Tsunoda et al. (2001) observed an increase in the low frequency to high frequency ratio of the heart rate variability after bright light exposure as well as after exposure to complete darkness. Besides heart rate variability, also cortisol shows a clear circadian rhythm with a peak around awakening (Kudielka and Kirschbaum, 2003). The circadian rhythm in cortisol is largely under the control of

the circadian pacemaker in the SCN (Buijs et al., 1999). Therefore, it is to be expected that the rhythm and the concentration of cortisol will be influenced by light. Indeed, Leproult et al. (2001) showed that in sleep deprived subjects 3 hours of bright light exposure (4500 lux) in the early morning (0500-0800) induced an increase in cortisol levels whereas afternoon (1300-1600) bright light exposure had no effect on cortisol. The cortisol peak after awakening is present in total darkness and can be enhanced by 1 hour of 800 lux applied at habitual time of waking (Scheer and Buijs, 1999). Thorn et al. (2004) showed that gradually increasing luminance levels (250 lux over 30 minutes) during awakening (dawn simulation) increased cortisol levels as compared to the control condition where subjects used their regular alarm clock to wake up, without additional increasing luminance. This increase in cortisol was accompanied by a higher level of reported arousal but not of reported stress.

Although the literature suggests that some of the variance in the responses to bright light may be associated with time of day, there is no straightforward analysis of such variation in human psychophysiological variables (Daurat et al., 1996; Rüger et al., 2002; Phipps-Nelson et al., 2003; Crowley et al., 2003). The fields of bright light application can range from clinical (light therapy of Seasonal Affective Disorder patients and sleep disorder patients) to work settings (improving work environment for shift workers) and it is crucial to know to what extent immediate effects of bright light on human psychophysiology are time-of-day-dependent.

For this reason we compared two datasets of daytime and nighttime bright light exposure, 12 hours out of phase with each other, in humans and their effects on sleepiness, fatigue, energy (psychological variables) and core body temperature, cortisol, and heart rate (physiological variables). 24 subjects participated in the two studies and were exposed to 4 hours of 5000 lux of bright light either between noon and 4 p.m. (daytime experiment) or between midnight and 4 a.m. (nighttime experiment).

Methods

Subjects

24 healthy male subjects participated in the two experiments, twelve in each (**daytime** experiment: mean age: 23.1 years, SD: 1.5 years, **nighttime** experiment: mean age: 21.8 years, SD: 1.9 years, no significant difference). Subjects were screened using a general health questionnaire and a Morningness-Eveningness-Questionnaire (Horne

and Östberg, 1976). Only healthy, non-smoking, subjects with intermediate MEQ scores (*i.e.* scores between 31 and 69) were selected. Subjects had to be without current medication or psychiatric illness; they neither worked night shifts nor did they recently (within the last month) travel more than one time zone. Subjects gave written informed consent and were paid for their participation. The medical ethics committee of Groningen University approved the protocol.

Time Isolation Facility

The protocol included either two stays of 1.5 days (experiment A: **daytime** bright light and dim light exposure) or three stays of 2.5 days (experiment B: **nighttime** bright light, dim light and extraocular light exposure) each in the time isolation facility. Results from the comparison of nighttime extraocular and ocular light exposure have been reported elsewhere (Rüger et al., 2003). The facility, where neither daylight nor clock information is present, can host four subjects simultaneously in separate rooms. Subjects could read or study, listen to music, watch videos, or perform other non-physical activities. Light sources present in the isolation facility did not exceed 10 lux measured at eye level and direction of gaze at any position in the room.

Consumption of tea, coffee, chocolate and bananas was not allowed because these substances influence serotonin concentration, which is the precursor of melatonin and furthermore, they may contaminate the saliva sample and therefore interfere with the results of the RIA used to determine the melatonin concentration (Gordijn et al., 1991).

Experimental Protocol

Experiment A (**daytime** bright light) took place from May until December 2001 and experiment B (**nighttime** bright light) from July until October 2000. For both experiments the time interval between sessions ranged from one week up to three weeks. In each session subjects were exposed to one of the two light treatments in counterbalanced order.

Both protocols are summarized in Figure 1. In experiment A, subjects entered the facility at 4 p.m. on day 0. Electrodes were fitted for recording EEG (2 channels C3-A2; C4-A1), EOG, EMG, and ECG. At the same time the test battery was introduced and explained and continuous measurement of rectal temperature started. At 6 p.m. of day 0 the first testing period (Testing 1) with hourly measurements started, including the test battery, six minutes of wake-EEG (3 min. eyes open followed by 3 min. eyes

closed) and ECG recording, and a saliva sample for the determination of cortisol concentration. Fifteen minutes prior to each test battery (duration: approximately 20 min.) subjects had to remain seated upright in their chair without moving as the change of position is known to influence hormonal concentrations (Deacon and Arendt, 1994). Warm meals were scheduled at the same time for all subjects, snacks and beverages were available on request. No consumptions were allowed in the 45 minutes interval prior to the collection of a saliva sample. After each consumption the subjects had to rinse their mouth with water to prevent contamination of the next saliva sample. At midnight subjects went to bed and the first sleep period (Sleep 1) was recorded. Subjects woke at 7 a.m. the following day (Day 1), had breakfast and a shower. The second testing period (Testing 2) started at 8 a.m., lasting till midnight. On day 1, subjects received either 5000 lux of bright light or less than 10 lux of dim light from noon till 4 p.m.. From midnight onwards, the second sleep period was recorded (Sleep 2), including spontaneous sleep termination, i.e. the subjects were instructed to sleep as long as they wanted and to give a sign via the intercom when they felt refreshed and wanted to get up.

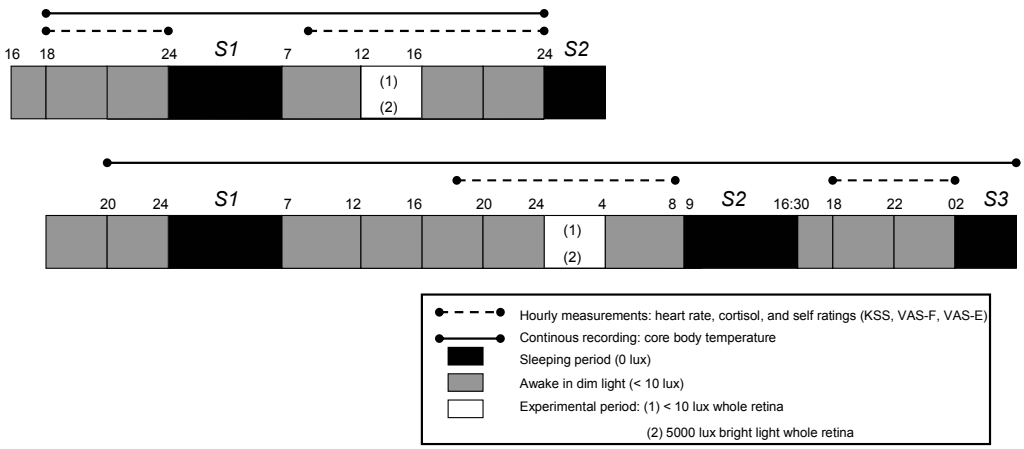


Figure 1. Experimental design of the two experiments. Upper part of the figure: daytime bright light experiment, lower part: nighttime experiment. Wake periods in dim light (<10 lux) are indicated by grey bars, sleeping periods by black bars (S1-S3), and periods of light exposure or dim light control by white bars. Solid lines indicate the periods of continuous measurements and hatched lines indicate the periods of hourly measurements.

In experiment B (nighttime) (see Rüger et al., 2003 for details) subjects entered the facility at 8 p.m. of day 0 and as in the daytime experiment, electrodes were fitted for recording EEG (2 channels C3-A2; C4-A1), EOG, and EMG. At the same time the test battery was introduced and explained and continuous recording of rectal temperature started. At midnight subjects went to bed and the first sleep period (Sleep 1) was recorded. The next morning (Day 1), subjects were woken up at 7 a.m., had breakfast and took a shower. Until 2 p.m. subjects were free to read or watch videos. Between 2 and 3 p.m. the EEG electrodes were checked and ECG electrodes were attached. At 3 p.m. the subjects practiced the test battery, and six minutes of wake-EEG (3 min. eyes open followed by 3 min. eyes closed) and ECG were recorded, and a saliva sample was collected for the determination of cortisol level. As in the daytime experiment, subjects remained seated upright prior to each test battery and no consumption was allowed during the 45 min. prior to the next saliva sample. The first testing period (Testing 1) with hourly measurements started at 6 p.m. and lasted till 8 a.m. the next morning (Day 2). During this period of sustained wakefulness, the subjects were exposed to 5000 lux of bright light or less than 10 lux of dim light from midnight until 4 a.m. (see below). From 9 a.m. till 4:30 p.m. (Day 2) the second sleep period (Sleep 2) was recorded. At 4:30 p.m. (Day 2) subjects were woken up again; they had breakfast and took a shower, and the second testing period (Testing 2) started which lasted till 2 a.m. of the next day (Day 3). From 2 a.m. onwards the third and last sleep period (Sleep 3) was recorded. Spontaneous sleep termination was recorded, *i.e.* subjects were instructed to sleep as long as they wanted and give a sign via the intercom when they felt refreshed and wanted to get up.

Light exposure

During both experiments, light intensity was <10 lux except for the period of light exposure (**daytime** experiment: noon till 4 p.m., **nighttime** experiment: midnight till 4 a.m.) and the sleeping periods (lights off = 0 lux). In both experiments we used Bright Light® boxes (Philips, Eindhoven, The Netherlands) which were placed vertically in front of the subject next to a computer screen. Subjects remained seated in front of the computer screen during the four hours of light exposure. Luminance was 5000 lux at eye level, measured in the direction of gaze. Subjects were exposed to the bright light or the dim light condition in a counter-balanced order.

Physiological parameters

1. Heart Rate

An electrocardiogram (ECG) was obtained using disposable, single-use, pre-gelled electrodes (Red Dot™, 3M Health Care, Borken, Germany) that were placed at the positions V6 and the right collarbone (bi-polar Wilson lead) of the subjects. The ground electrode was the same used for the EEG recordings, which was placed on the forehead of the subjects. ECG and EEG was recorded hourly for 6 min. (3 min. with eyes open and 3 min. with eyes closed) during the testing periods. Heart rate was calculated as beats per minute, dividing the total amount of heart beats of each of the 3-minutes periods by three. There was no significant difference between the data from the two 3-minutes periods (eyes closed and eyes open), therefore we present the combined data.

2. Cortisol

Cortisol concentrations were measured in saliva. Subjects gave a saliva sample prior to each test battery, *i.e.* once per hour. Saliva was collected using Sarstedt Salivettes® with a polyester swab. Samples were centrifuged immediately and stored at –20 °C. Cortisol concentration was determined using a RIA immunoassay (Spectria®, Cortisol [^{125}I], Coated Tube Radioimmunoassay by Orion Diagnostics, Espoo, Finland). The mean value of duplicate samples was taken for the cortisol concentration. The limit of detection for the cortisol RIA was 0.8 nmol/l with an intra-assay variation of 7.5 % at a low concentration (4.1 nmol/L) and 4.0 % (16.5 nmol/L) at a high concentration. The inter-assay variation was 8.6 % at a low concentration (4.1 nmol/L) and 4.9 % at a high concentration (16.6 nmol/L).

3. Core body temperature

Core body temperature was recorded by a rectal probe. The thermometer was connected to a portable registration system (JOBLOG, Bakker & Beersma, 1991) which records temperature at one-minute intervals with a resolution of 0.05° C. Data on core body temperature (CBT) were occasionally missing due to sanitary requirements or technical failure. Missing data of less than 90 min. were reconstructed by linear interpolation. Missing data of more than 90 min. were recorded as missing. Only subjects with complete datasets in both conditions were included in the

temperature analysis. This resulted in a sample size of ten subjects for the daytime experiment and seven subjects for the nighttime experiment.

Psychological parameters: test battery (sleepiness, fatigue, and energy)

The subjective feelings of sleepiness, fatigue, and energy were assessed by the use of three questionnaires, the Karolinska Sleepiness Scale (KSS) (Åkerstedt and Gillberg, 1990) and the Visual Analogue Scale for Fatigue and Energy (VAS-F and VAS-E) (Lee et al., 1991). Every hour subjects completed the questionnaires electronically on a test-computer, from which the clock function was disabled.

Statistical Analysis

The activating effects of bright light were tested using repeated measures ANOVAs for the within-subjects factors **condition** (*dim* versus *bright light*), **exposure** (*before* versus *during* the light exposure), and **time** (daytime experiment: *9, 10, 11 a.m.* versus *1, 2, 3 p.m*., nighttime experiment: *9, 10, 11 p.m.* versus *1, 2, 3 a.m*.) and the between-subject factor **experiment** (*daytime bright light exposure* versus *nighttime bright light exposure*). To answer the question whether light *per se* has an effect on psychological and physiological parameters, the effect of the interaction between **condition** and **exposure** is the relevant measure. It tells us whether the variable under study changes during light exposure relative to the preceding dim interval, and whether this change differs from the condition in which no light was applied at all. To answer the question if the effect of light is dependent on time-of-day, the interaction effect of **condition**, **exposure**, and **experiment** was determined. Where interactions contributed significantly to the explained variance, post-hoc ANOVAs were calculated to determine the direction of the effect.

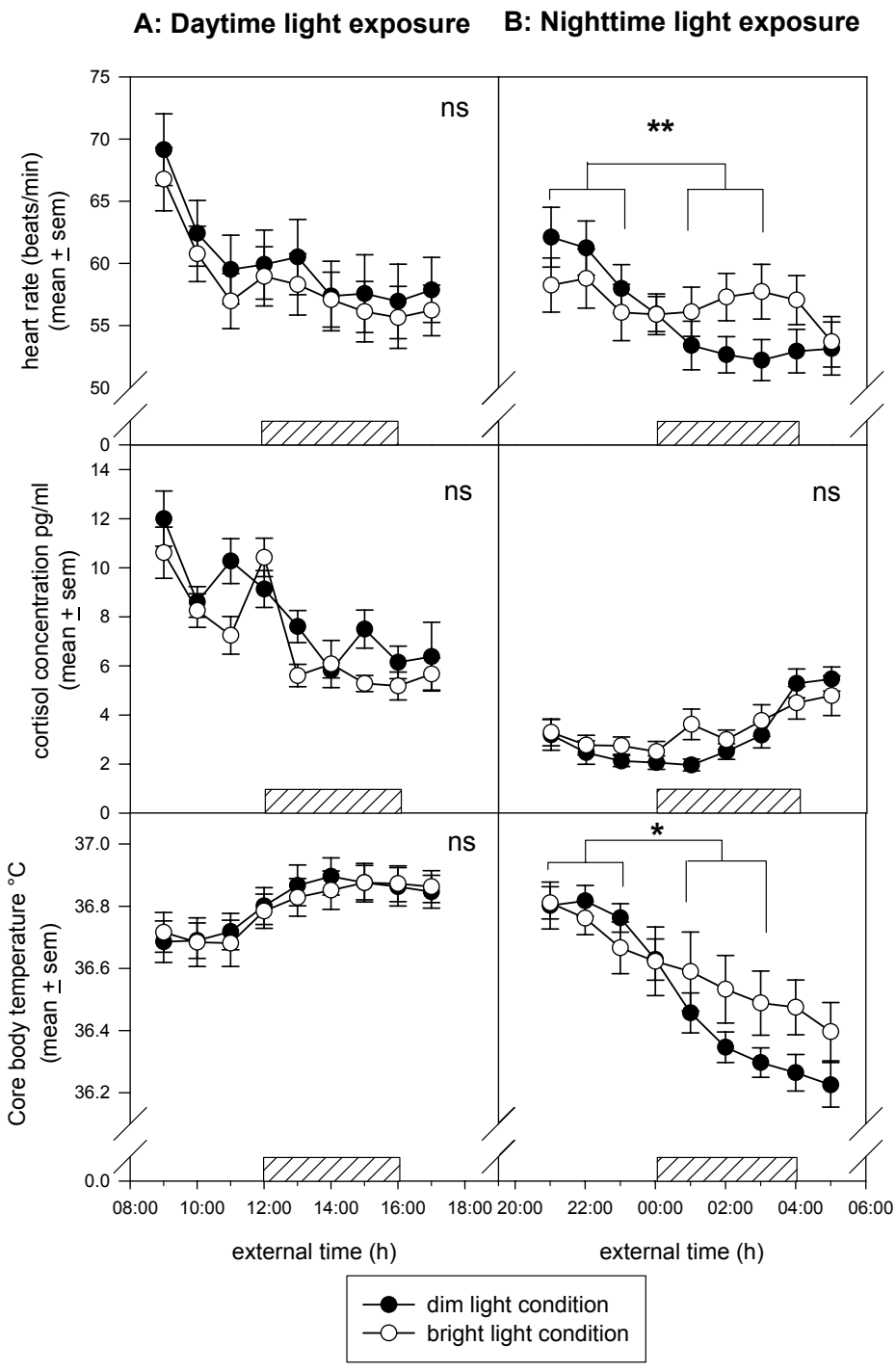
Results

Figure 2 shows the results of daytime (left panels) versus nighttime (right panels) bright light exposure for the physiological variables heart rate, cortisol, and core body temperature (top to bottom). The upper two panels show the changes in heart rate for the two experiments, before and during the light exposure. There was an effect of light on heart rate (interaction effects for the factors condition and exposure, $F(1,22) = 13.0$, $p = 0.002$). This effect depended on the time of day (three-way interaction of the factors condition, exposure, and experiment, $F(1, 22) = 7.9$, $p = 0.010$). Post-hoc ANOVAs showed that bright light exposure significantly increased heart rate during nighttime ($F(1, 11) = 22.9$, $p = 0.001$), but not during daytime ($F(1, 11) = 0.2$, $p = 0.604$).

The two panels in the middle show the cortisol concentration for both experiments, before and during the light exposure. Light had no significant effect on cortisol (interaction effect for the factors condition and exposure, $F(1, 22) = 0.9$, $p > 0.1$), independent of the time of day (three-way interaction for the factors condition, exposure, and experiment, $F(1, 22) = 0.1$, $p > 0.1$).

The lower two panels show the courses of core body temperature during the two experiments, before and during the light exposure. As for heart rate, there was an overall effect of light on CBT (interaction effect for condition and exposure, $F(1, 15) = 4.5$, $p = 0.05$) and this effect of light did depend on the time of day ($F(1, 15) = 7.2$, $p = 0.017$). Post hoc ANOVAs revealed that CBT increased in bright light exposure as compared to dim light during nighttime ($F(1, 6) = 6.1$, $p = 0.048$), but not during daytime ($F(1, 9) = 0.3$, $p = 0.586$).

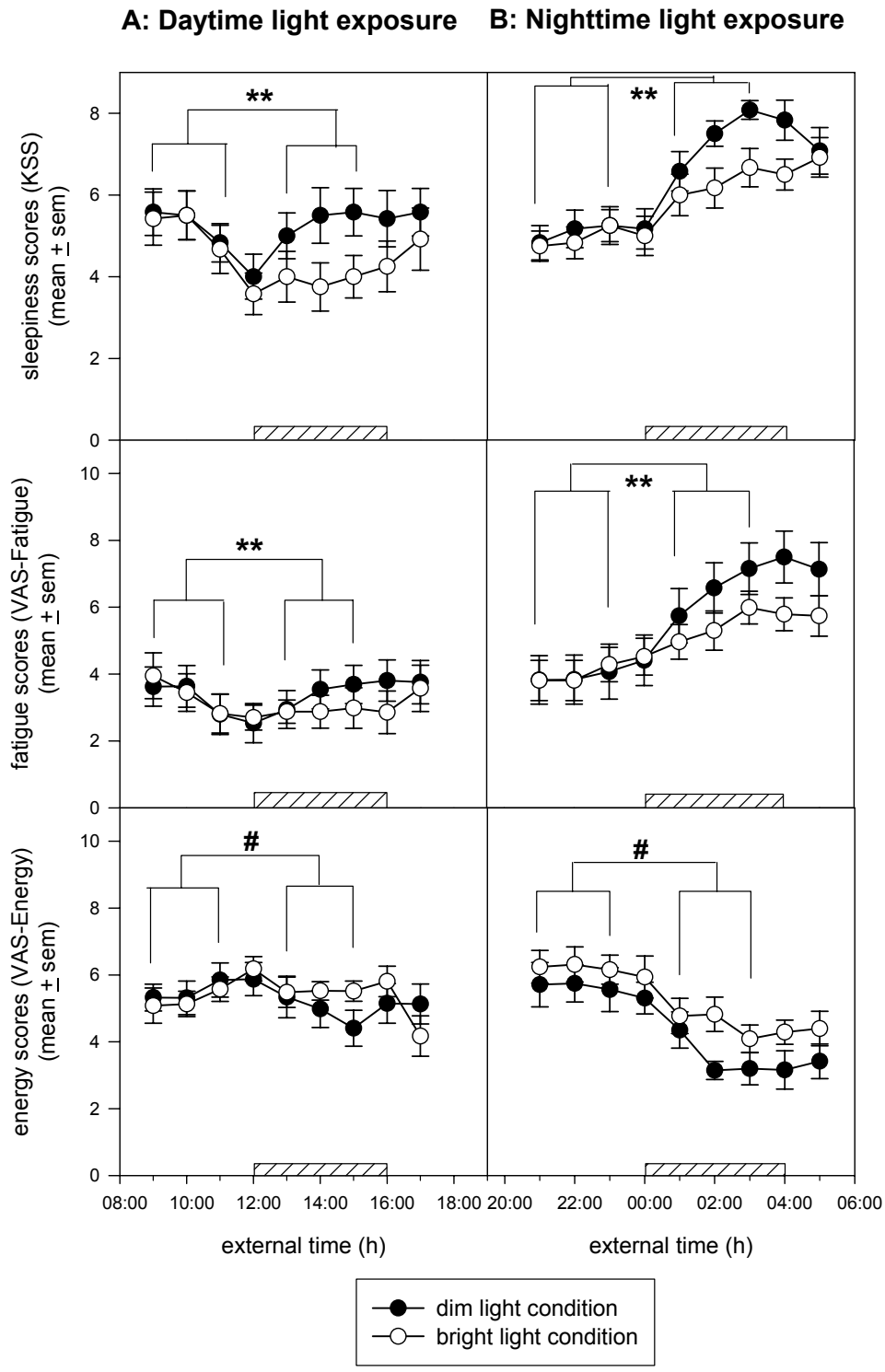
Figure 2. The course of heart rate, cortisol concentration, and core body temperature for the two experiments, before and during bright light exposure versus dim light. The hatched bars indicate the period of light exposure (**daytime** experiment: noon till 4 p.m., **nighttime** experiment: midnight till 4 a.m.). Repeated measures ANOVA for the three hours before (daytime experiment: 9, 10, 11 a.m., nighttime experiment: 9, 10, 11 p.m.) versus during the experimental condition (daytime experiment:1, 2, 3 p.m., nighttime experiment: 1, 2, 3 a.m.) revealed a significant condition effect of the bright light on heart rate ($p = 0.010$) and core body temperatur ($p = 0.017$) depending on the time of day, but no effect on cortisol ($p = 0.727$). Significances indicated in the figure refer to post-hoc ANOVAs for the day-time and night-time experiments separately (* denotes $p<0.05$, ** denotes $p<0.01$)


A: Daytime light exposure
B: Nighttime light exposure
heart rate (beats/min)
(mean ± sem)
cortisol concentration pg/ml
(mean ± sem)
Core body temperature °C
(mean ± sem)
ns
**
*
external time (h)
external time (h)
dim light condition
bright light condition

In Figure 3 the effects of daytime (left panels) and nighttime (right panels) bright light exposure on the three psychological variables sleepiness, fatigue, and energy are depicted. The two upper panels show a clear reduction of subjective sleepiness as measured by the KSS for the daytime as well as for the nighttime bright light exposure (interaction effect for the factors condition and exposure, $F(1, 22) = 16.8$, $p < 0.001$). This alerting effect of bright light exposure is independent of the time of day at which light is presented (three-way interaction effect for the factors condition, exposure, and experiment, $F(1, 22) = 0.4$, $p = 0.527$).

The course of subjective fatigue as measured by the VAS-F during daytime and nighttime bright light exposure follows a similar pattern as subjective sleepiness, *i.e.* subjects in the bright light group report to feel less fatigued during the light exposure than before compared to the dim light group (interaction effect for factors condition and exposure, $F(1, 22) = 8.3$, $p = 0.008$). As for subjective sleepiness, the effect of bright light on subjective fatigue is independent of time of day (three-way interaction of condition, exposure, and experiment, $F(1, 22) = 0.8$, $p = 0.372$). The two lower panels depict the course of the subjective feeling of energy as measured by the VAS-E for the daytime and nighttime experiment, before and during the light exposure. As expected, the energy ratings show the reversed pattern of subjective sleepiness and fatigue, *i.e.*, in both experiments the subjects report on average to feel more energetic during the light exposure in the bright light condition than in the dim light condition. This interaction effect of condition and exposure was not significant ($F(1, 22) = 3.6$, $p = 0.071$). Again the effect was independent of the time the light was given ($F(1, 22) = 0.4$, $p = 0.503$).

Figure 3. The course of subjective sleepiness, fatigue, and energy for the two experiments, before and during bright light exposure versus dim light. The hatched bars indicate the period of light exposure (daytime experiment: noon till 4 p.m., nighttime experiment: midnight till 4 a.m.). Repeated measures ANOVA for the three hours before (daytime experiment: 9, 10, 11 a.m., nighttime experiment: 9, 10, 11 p.m.) versus during the experimental condition (daytime experiment:1, 2, 3 p.m., nighttime experiment: 1, 2, 3 a.m.) revealed a signicant condition effect of the bright light on sleepiness ($p = 0.001$) and fatigue ($p = 0.008$), and a trend for energy $p = 0.071$). The effects turned out to be independent of the time of day. (** denotes $p<0.01$, # denotes $p<0.1$)


A: Daytime light exposure
B: Nighttime light exposure
sleepiness scores (KSS)
(mean ± sem)
fatigue scores (VAS-Fatigue)
(mean ± sem)
energy scores (VAS-Energy)
(mean ± sem)
**
#
08:00
10:00
12:00
14:00
16:00
18:00
20:00
22:00
00:00
02:00
04:00
06:00
external time (h)
dim light condition
bright light condition

Discussion

To answer the question which effects of bright light exposure on human psychophysiology are time-of-day dependent, we compared 4 hours of daytime with 4 hours of nighttime bright light exposure on heart rate, cortisol, core body temperature, sleepiness, fatigue, and energy.

Concerning the physiological variables heart rate and core body temperature we found an overall effect of light that was time-of-day dependent, *i.e.* nighttime bright light exposure increased heart rate and reduced the circadian drop in core body temperature, whereas daytime bright light exposure did increase neither heart rate nor core body temperature. The heart rate results are in accordance with the results of Scheer et al. (1999) who showed an increase in heart rate in response to bright light (20 min of 100 and 800 lux respectively) during the nighttime (ZT20 after habitual wake time, range of wake time: 06:15-08:30) and no effect on heart rate during daytime. Cajochen and colleagues (Cajochen et al., 2005) exposed their subjects from 21:30-23:30 to short wavelength light (460nm) and found an increase in heart rate. They also found an increase of core body temperature which resembles our current results and the findings of Badia et al. (1991), that nighttime bright light exposure elevates core body temperature.

The lack of effects of bright light on cortisol concentrations during the daytime might be due to our timing of the light exposure. The light exposure period was from noon till 4 p.m., whereas Leproult et al. (2001) exposed their subjects from 05:00-08:00 to 4000 lux of bright light, Scheer et al. (1999) between 05:45-07:30 to one hour of 800 lux, and Thorn et al. (2004) used a dawn simulator (250 lux over 30 minutes) during awakening (mean awakening time: 06:40) to increase cortisol; all periods of exposure in the range of the morning cortisol peak (Kudielka and Kirschbaum, 2003). Apart from observing no effect of daytime bright light exposure on cortisol, we also found no effect on melatonin (Rüger et al., 2002) which is in accordance with the findings of Leproult and colleagues (2001) and Phipps-Nelson et al. (2003). Leproult and colleagues (2001) exposed their subjects to afternoon light (13:00-16:00) and found no effect on cortisol and melatonin. In the study of Phipps-Nelson, the period of light exposure was noon till 5 p.m. and they also found no effect on melatonin.

We found no time-of-day-dependent effect of light on the three (related) psychological variables we measured (sleepiness, fatigue, and energy). This means that bright light elicited its alerting and sleepiness-reducing properties independent of the timing of exposure. Due to the fact that there is almost no melatonin secreted during

daytime, which therefore cannot be suppressed by light, this means that there must be an alternative mechanism or pathway by which light immediately influences alertness in humans. Despite the results of Kräuchi and colleagues (Kräuchi et al., 1998; Kräuchi and Wirz-Justice, 2001), showing a functional link between the degree of heat loss (distal vasodilatation) and subjective sleepiness (measured by the KSS), we found a reduction of subjective sleepiness in the absence of any effect of daytime light on core body temperature. Indicating again that light affects human alertness in another way besides the mechanisms of melatonin suppression and/or elevation of core body temperature.

Evidence in favor of such an alternative pathway of light altering psychological states comes from neuroanatomic animal studies which show indirect projections from the SCN to brain areas that are strongly associated with the regulation of sleep-wake processes. Aston-Jones et al. (2001) found a neural circuit in the rat, that proved the locus coeruleus to be a target area of indirect projections from the SCN via the dorsomedial hypothalamic nucleus. By performing lesions of the dorsomedial hypothalamic nucleus, which eliminated circadian variations in the locus coeruleus, they showed the functionality of this circuit. The locus coeruleus is associated with sleep-wake regulatory processes (Lu et al., 2000). Recently, Deurveilher et al. (Deurveilher et al., 2002; Deurveilher and Semba, 2005) showed that the medial preoptic area, the subparaventricular zone, and the dorsomedial hypothalamic nucleus might not only serve as relays to sleep-promoting nuclei such as the ventrolateral and the medial preoptic nuclei, but also to wake-regulatory brain areas such as the locus coeruleus. Furthermore, Lu et al (1999) identified a set of sleep-active cells in the ventrolateral preoptic nucleus of rats that receive direct luminance signals from the retina. The ventrolateral preoptic nucleus also belongs to the target regions for the projections from intrinsically photosensitive retinal ganglion cells, which contribute to circadian entrainment, pupillary light reflex, and the regulation of sleep-wake states (Gooley et al., 2003). In humans, the locus coeruleus appears to be one of the possible candidate nuclei that was influenced by bright light exposure during the nighttime as Perrin and colleagues (2004) showed in their PET study, using regional blood flow as an activation-deactivation marker of brain areas.

Concerning the primary question to what extent immediate effects of bright light on human psychophysiology are time-of-day dependent, we conclude that the measured effects on the psychological variables during daytime are not significantly different from those during nighttime bright light exposure. This cannot simply be

explained by the changes in heart rate and core body temperature, as these variables do not change in any systematic way in response to light during the daytime.

We are aware that our comparison includes only two circadian phases, and a limited number of variables. Yet, the results clearly demonstrate that psychological responses to light are similar when comparing light exposures around midnight with midday, while physiological variables thought to be related to those psychological reactions behave quite differently. Apparently, the regulation of human alertness is more complex than has been estimated so far. Given the importance of alertness for performance, the mechanisms behind these differential light effects need to be discovered.

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References

Åkerstedt T and Gillberg M (1990) Subjective and objective sleepiness in the active individual. Int J Neurosci 52:29-37.

Aston-Jones G, Chen S, Zhu Y, and Oshinsky ML (2001) A neural circuit for circadian regulation of arousal. Nat Neurosci 4:732-738.

Badia P, Culpepper J, Myers B, Boecker M, and Harsh J (1990) Psychophysiological and behavioral effects of bright and dim light. Sleep:387-387

Badia P, Myers B, Boecker M, Culpepper J, and Harsh JR (1991) Bright light effects on body temperature, alertness, EEG and behavior. Physiol Behav 50:583-588.

Badia P, Myers B, and Murphy P (1993) Melatonin and Thermoregulation, in *Melatonin: Biosynthesis, Physiological Effects, and Clinical Applications*, Reiter R and Yu H-S, eds, pp CRC Press, Boca Raton, Fl

Beersma DG and Daan S (1993) Strong or weak phase resetting by light pulses in humans? J Biol Rhythms 8:340-347.

Buijs RM, Wortel J, Van Heerikhuize JJ, Feenstra MG, Ter Horst GJ, Romijn HJ, and Kalsbeek A (1999) Anatomical and functional demonstration of a

multisynaptic suprachiasmatic nucleus adrenal (cortex) pathway. Eur J Neurosci 11:1535-1544.

Burgess HJ, Sletten T, Savic N, Gilbert SS, and Dawson D (2001) Effects of bright light and melatonin on sleep propensity, temperature, and cardiac activity at night. J Appl Physiol 91:1214-1222.

Cajochen C, Munch M, Kobialka S, Krauchi K, Steiner R, Oelhafen P, Orgul S, and Wirz-Justice A (2005) High sensitivity of human melatonin, alertness, thermoregulation, and heart rate to short wavelength light. J Clin Endocrinol Metab 90:1311-1316.

Cajochen C, Zeitzer JM, Czeisler CA, and Dijk DJ (2000) Dose-response relationship for light intensity and ocular and electroencephalographic correlates of human alertness. Behav Brain Res 115:75-83.

Campbell SS and Dawson D (1990) Enhancement of nighttime alertness and performance with bright ambient light. Physiol Behav 48:317-320.

Campbell SS, Dijk DJ, Boulos Z, Eastman CI, Lewy AJ, and Terman M (1995) Light treatment for sleep disorders: consensus report. III. Alerting and activating effects. J Biol Rhythms 10:129-132.

Crowley SJ, Lee C, Tseng CY, Fogg LF, and Eastman CI (2003) Combinations of bright light, scheduled dark, sunglasses, and melatonin to facilitate circadian entrainment to night shift work. J Biol Rhythms 18:513-523.

Daurat A, Aguirre A, Foret J, Gonnet P, Keromes A, and Benoit O (1993) Bright light affects alertness and performance rhythms during a 24-h constant routine. Physiol Behav 53:929-936.

Daurat A, Foret J, Touitou Y, and Benoit O (1996) Detrimental influence of bright light exposure on alertness, performance, and mood in the early morning. Neurophysiol Clin 26:8-14.

Dawson D and Campbell SS (1991) Timed exposure to bright light improves sleep and alertness during simulated night shifts. Sleep 14:511-516.

Deacon S and Arendt J (1994) Posture influences melatonin concentrations in plasma and saliva in humans. Neurosci Lett 167:191-194.

Deurveilher S, Burns J, and Semba K (2002) Indirect projections from the suprachiasmatic nucleus to the ventrolateral preoptic nucleus: a dual tract-tracing study in rat. Eur J Neurosci 16:1195-1213.

Deurveilher S and Semba K (2005) Indirect projections from the suprachiasmatic nucleus to major arousal-promoting cell groups in rat: Implications for the circadian control of behavioural state. Neuroscience 130:165-183.

Foret J, Daurat A, and Tirilly G (1998) Effect of bright light at night on core temperature, subjective alertness and performance as a function of exposure time. Scand J Work Environ Health 1998;24 Suppl 3:115-120.

Gilbert SS, van den Heuvel CJ, and Dawson D (1999) Daytime melatonin and temazepam in young adult humans: equivalent effects on sleep latency and body temperatures. J Physiol 514 (Pt 3):905-914.

Gooley JJ, Lu J, Fischer D, and Saper CB (2003) A broad role for melanopsin in nonvisual photoreception. J Neurosci 23:7093-7106.

Gordijn MCM, Jansen JHC, Medema HM, Flentge F, and Beersma DGM (1991) Melatonin in saliva, effect of toothpaste, coffee, smoking and lipstick. Sleep Res 20A:493.

Honma K and Honma S (1988) A human phase response curve for bright light pulses. Jpn J Psychiatry Neurol 42:167-168.

Horne JA and Östberg O (1976) A self-assessment questionnaire to determine morningness- eveningness in human circadian rhythms. Int J Chronobiol 4:97-110.

Khalsa SB, Jewett ME, Cajochen C, and Czeisler CA (2003) A phase response curve to single bright light pulses in human subjects. J Physiol 549:945-952.

Kräuchi K, Cajochen C, and Wirz-Justice A (1998) Circadian and homeostatic regulation of core body temperature and alertness in humans: what is the role of melatonin?, in *Circadian Clocks and Entrainment*, Honma KI and Honma S, eds, pp 131-146, Hokkaido University Press, Sapporo

Kräuchi K and Wirz-Justice A (2001) Circadian clues to sleep onset mechanisms. Neuropsychopharmacology 25:S92-S96.

Kudielka BM and Kirschbaum C (2003) Awakening cortisol responses are influenced by health status and awakening time but not by menstrual cycle phase. Psychoneuroendocrinology 28:35-47.

Lee KA, Hicks G, and Nino-Murcia G (1991) Validity and reliability of a scale to assess fatigue. Psychiatry Res 36:291-298.

Leproult R, Colecchia EF, L'Hermite-Baleriaux M, and Van Cauter E. (2001) Transition from dim to bright light in the morning induces an immediate elevation of cortisol levels. J Clin Endocrinol Metab 86:151-157.

Lewy AJ, Wehr TA, Goodwin FK, Newsome DA, and Markey SP (1980) Light suppresses melatonin secretion in humans. Science 210:1267-1269.

Lu J, Greco MA, Shiromani P, and Saper CB (2000) Effect of lesions of the ventrolateral preoptic nucleus on NREM and REM sleep. J Neurosci 20:3830-3842.

Lu J, Shiromani P, and Saper CB (1999) Retinal input to the sleep-active ventrolateral preoptic nucleus in the rat. Neuroscience 93:209-214.

Minors DS, Waterhouse JM, and Wirz-Justice A (1991) A human phase-response curve to light. Neurosci Lett 133:36-40.

Myers BL and Badia P (1993) Immediate effects of different light intensities on body temperature and alertness. Physiol Behav 54:199-202.

Partonen T and Lonnqvist J (2000) Bright light improves vitality and alleviates distress in healthy people. J Affect Disord 57:55-61.

Perrin F, Peigneux P, Fuchs S, Verhaeghe S, Laureys S, Middleton B, Degueldre C, Del FG, Vandewalle G, Balteau E, Poirrier R, Moreau V, Luxen A, Maquet P, and Dijk DJ (2004) Nonvisual responses to light exposure in the human brain during the circadian night. Curr Biol 14:1842-1846.

Phipps-Nelson J, Redman JR, Dijk DJ, and Rajaratnam SM (2003) Daytime exposure to bright light, as compared to dim light, decreases sleepiness and improves psychomotor vigilance performance. Sleep 26:695-700.

Rüger M, Gordijn MC, Beersma DG, de Vries B, and Daan S (2002) Bright light effects at night and day on various measures of sleepiness, in *Sleep-Wake Research in the Netherlands*, Van Bemmel AL, Beersma DG, Hofman WF, Ruigt GSF, and Vos PJE, eds, pp 95-99,

Rüger M, Gordijn MC, Beersma DG, de Vries B, and Daan S (2003) Acute and phase-shifting effects of ocular and extraocular light in human circadian physiology. J Biol Rhythms 18:409-419.

Rüger M, Gordijn MC, Beersma DGM, de Vries B, and Daan S (2005) Weak relationships between suppression of melatonin and suppression of sleepiness/fatigue in response to light exposure. J Sleep Res

Saito Y, Shimizu T, Takahashi Y, Mishima K, Takahashi K, Ogawa Y, Kogawa S, and Hishikawa Y (1996) Effect of bright light exposure on muscle sympathetic nerve activity in human. Neurosci Lett 219:135-137.

Scheer FA and Buijs RM (1999) Light affects morning salivary cortisol in humans. J Clin Endocrinol Metab 84:3395-3398.

Scheer FA, Van Doornen LJ, and Buijs RM (1999) Light and diurnal cycle affect human heart rate: possible role for the circadian pacemaker. J Biol Rhythms 14:202-212.

Thorn L, Hucklebridge F, Esgate A, Evans P, and Clow A (2004) The effect of dawn simulation on the cortisol response to awakening in healthy participants. Psychoneuroendocrinology 29:925-930.

Tsunoda M, Endo T, Hashimoto S, Honma S, and Honma KI (2001) Effects of light and sleep stages on heart rate variability in humans. Psychiatry Clin Neurosci 55:285-286.